(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 357 009 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **02.03.94**

(51) Int. Cl.[5]: **C12P 41/00**, C12P 7/62, C12P 13/00, C12P 17/02, C12P 9/00, C12P 19/02, C12P 19/44

(21) Application number: **89115956.8**

(22) Date of filing: **30.08.89**

(54) **Method of resolution of hydroxy-cyclopentenones using a lipase and transacylation agents.**

(30) Priority: **30.08.88 US 238358**
24.08.89 US 396723

(43) Date of publication of application:
07.03.90 Bulletin 90/10

(45) Publication of the grant of the patent:
02.03.94 Bulletin 94/09

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 337 920

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(73) Proprietor: **G.D. Searle & Co.**
P.O. Box 5110
Chicago Illinois 60680(US)

(72) Inventor: **Wong, Chi-Huey**
1208 Haddox, USA-College Station
Texas 77840(US)
Inventor: **Wang, Yi-Fong**
200 Avenue A, 7-D, USA-College Station
Texas 77840(US)
Inventor: **Hennen, William J.**
2306 Long Drive
USA-Bryan, Texas 77802(US)
Inventor: **Babiak, Kevin Anthony**
2216 Central Street, Apt.3S
USA Evanston, Illinois 60201(US)
Inventor: **DYGOS, John H.**
2645 Crabtree Lane
Northbrook, Illinois 60062(US)
Inventor: **NG, John S.**
341 West 30th place
Chicago, Illinois 60616(US)

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(74) Representative: Bell, Hans Chr., Dr. et al
BEIL, WOLFF & BEIL,
Rechtsanwälte,
Postfach 80 01 40
D-65901 Frankfurt (DE)

Description

The present invention relates to an enzymatic resolution method for preparing chiral hydroxycyclopentenones by lipase catalyzed irreversible transesterification using enol esters as transacylation reagents.

Hydrolytic enzymes such as lipases, esterases, and proteases have been used extensively as catalysts in enantioselective syntheses. Whitesides, G.M., Wong, C-H. Angew. Chem. Int. Ed. Engl. 24 (1985) 617; Jones, J.B. Tetrahedron 42 (1986) 3351; Roberts, S.M. Chem. Br. (1987) 127; Akiyama, A., Bednarski, M., Kim, M.J., Simon, E.S., Waldmann, H.I., Whitesides, G.M. Ibid. (1987) 645. Because of their relatively high stability in organic media, many hydrolytic enzymes also can be used in organic solvents for certain types of transformations which are difficult to do in water. The most common reactions are esterase and lipase-catalyzed stereoselective esterifications and transesterifications. Klibanov, A.M. CHEMTECH (1986) 354-9; Klibanov, A.M., Cambou, B. J. Am. Chem. Soc. 106 (1984) 2687-92. Chen, C-S., Wu, S-H., Girdaukas, G., Sih, C.J. J. Am. Chem. Soc. 109 (1987) 2812-17; Guo, Z.W., Sih, C.J. Ibid. 110 (1988) 1999-2001; Gil, G., Ferre, E., Meou, A., Petit, J.L., Triantaphylides, C. Tetrahedron Lett. 28 (1987) 1647; Yokozeki, K., Yamanaka, S., Takinami, K., Hirose, Y., Tanaka, A., Sonomoto, K., Fukui, S. Eur. J. Appl. Microbiol. Biotechnicol 14 (1982) 1; Tambo, G.M.R., Schar, H-P., Busquets, X.F., Ghisalba, O. Tetrahedron Lett. 27 (1986) 5705-10; Belan, A., Bolte, J., Fauve, A., Gourey, J.G., Veschambre, H. J. Org. Chem. 52, 256-60. Langrand, G., Baratti, J., Buono, G., Triantaphylides, C. Tetrahedron Lett. 27 (1986) 29-32.

One disadvantage of enzyme catalyzed hydrolytic reactions is that they are very slow compared to simple hydrolyses. Langrand, G., Baratti, J., Buono, G., Triantaphylides, C. Tetrahedron Lett. 27 (1986) 29-32. In addition, the products produced by enzymatic hydrolyses very often have to be separated from other by-products (particularly alcohol generated from the acylating reagent). Due to the reversible nature of these reactions, and due to the same stereoselectivity of the enzyme catalysis in both directions, the optical purity of the product obtained decreases as the reverse reaction proceeds. This situation is illustrated in FIG. 1 where a racemic alcohol is to be resolved via an enzymatic esterification (R" = H) or transesterification.

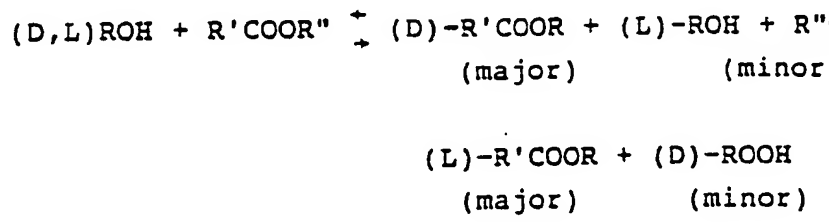


FIG. 1

As shown in FIG. 1, if the D-isomer is a better substrate than the L-isomer for the enzyme, accumulation of the D-ester and the unreactive L-alcohol will be observed. In the reverse reaction, however, the D-ester is a better substrate and will be converted to the D-alcohol. The enantiomeric excess of both the D-ester and the L-alcohol therefore will decrease progressively as the extent of the reverse reaction increases. This reverse reaction problem clearly has been illustrated in the kinetic resolution of menthol, Chen, C-S., Wu, S-H., Girdaukas, G., Sih, C.J. J. Am. Chem. Soc. 109 (1987) 2812-17; Guo, Z.W., Sih, C.J. Ibid. 110 (1988) 1999-2001, and can be seen in the enantioselective esterification or transesterification of meso compounds.

SUMMARY OF THE INVENTION

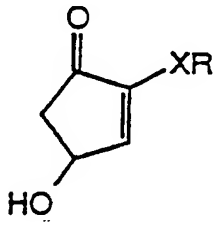
The method of the present invention blocks the progress of the reverse reaction. The present invention is a process for irreversible regio- and stereoselective enzyme catalyzed acylation of alcohols using enol esters as acylating reagents. The present invention permits the selective modification of hydroxyl group(s) of chiral hydroxycyclopentenones.

The simplicity of this irreversible transesterification makes the operation useful for the preparation of chiral alcohols or esters that may be difficult to prepare by other means.

Enzymatic Resolution of Hydroxycyclopentenones Utilizing Lipase

Lipase catalyzed reactions were utilized in the resolution of hydroxycyclopentenones as illustrated in the following reaction schemes, illustrating specific embodiments of the present invention.

Using the procedure described herein, resolution of hydroxy-cyclopentenones was achieved. Specifically, hydroxy-alkyl-carbonyl-alkyl, alkenyl or alkynyl cyclopentenones, alternatively including a heteroatom in the side chain, are suitable for practice of the described method. The compounds can be described illustratively by the formula:

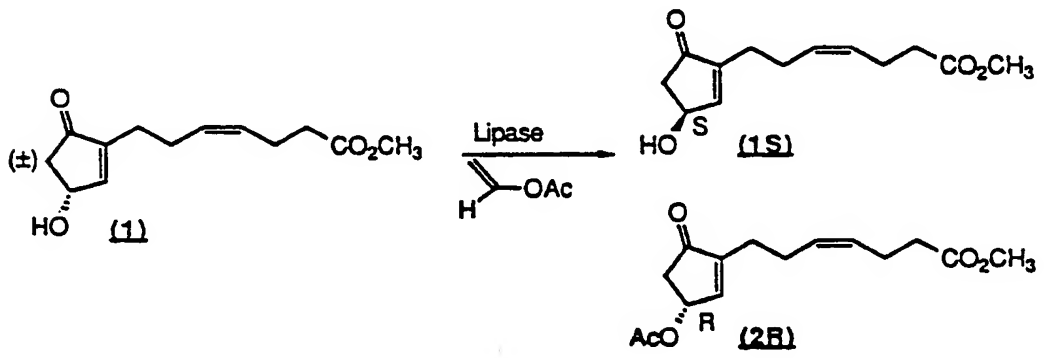


wherein X represents alkyl, alkenyl or alkynyl, of from 2 to 10 carbon atoms, alternatively including a heteroatom, namely S or O, at the 2, 3, 4, 5, 6, 7, 8 or 9 position; and R is CH_2OR, wherein R is hydrogen, alkyl of 1 to 6 carbon atoms, tetrahydropyranyl, ethoxyethyl, acyl or CO_2R_2 or $(R_3)_3Si$ wherein R_2 is alkyl of 1 to 6 carbon atoms and R_3 is alkyl of 1 to 10 carbon atoms or aryl.

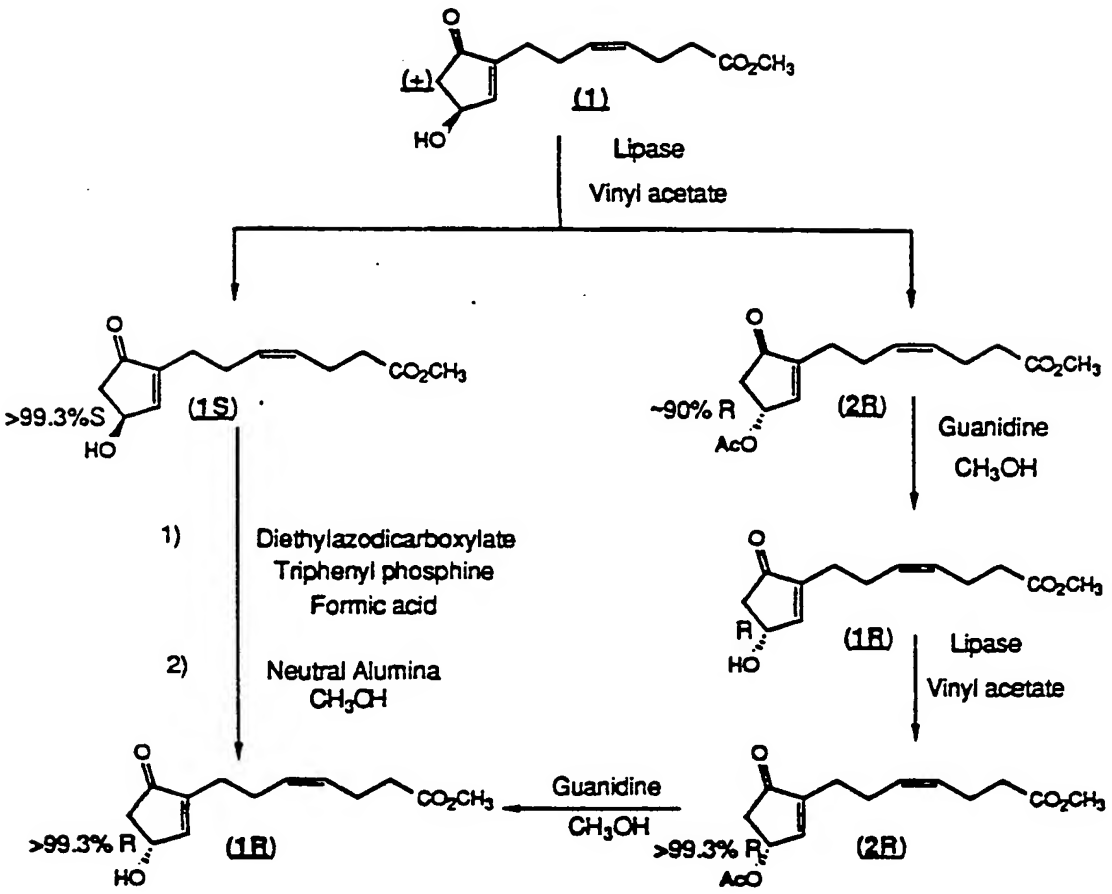
Practical and presently preferred embodiments of the method are described in the following examples.

Several lipases which are available commercially were utilized, namely: Candida cylindracea (CC), Pseudomonas Species (P.Sp.), porcine pancreatic lipase (PPL), all from Sigma Chemical, and Amano P, ANL, Aspergilus Niger, ChE, Cholesterol Esterase, all from Amano Co. The role of solvent with respect to both rate of reaction and extent of kinetic resolution was also studied. The conversions were monitored utilizing normal phase HPLC on silica gel (Zorbax sil) and the optical purities of products were analyzed using HPLC on chiral stationary phase (Chiracel OD column).

Scheme I



SCHEME 2



A preferred lipase among the above mentioned is porcine pancreatic lipase or amano P.

Preferred acylating agents are isopropenyl acetate, isopropenyl valerate, vinyl acetate, vinyl propionate and vinyl valerate and among these especially isopropenyl acetate or vinyl acetate.

Furthermore the method is especially useful when porcine pancreas (PPL) is the lipase, vinylacetate as acylating compound and the compound for resolution is

Methyl 7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate (1S)
Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-4-heptenoate (4)
3-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-propyne (5)
Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-5Z-heptenoate (6) or
Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-heptenoate (7)

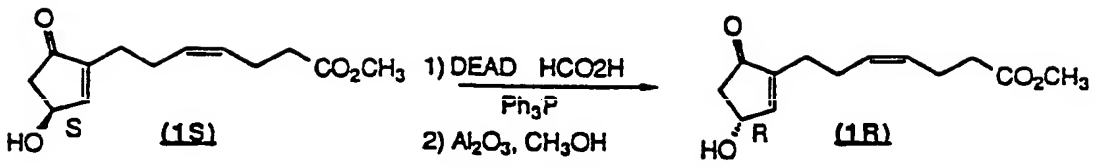
or mostly preferred methyl 7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate.

Furthermore the lipase may be immobilized on a support.

Preferred solvents which may be used in the method of the present invention are toluene, t-butylmethyl ether, tetrahydrofuran, diethyl ether, hexane and most preferred $CHCl_3$, benzene.

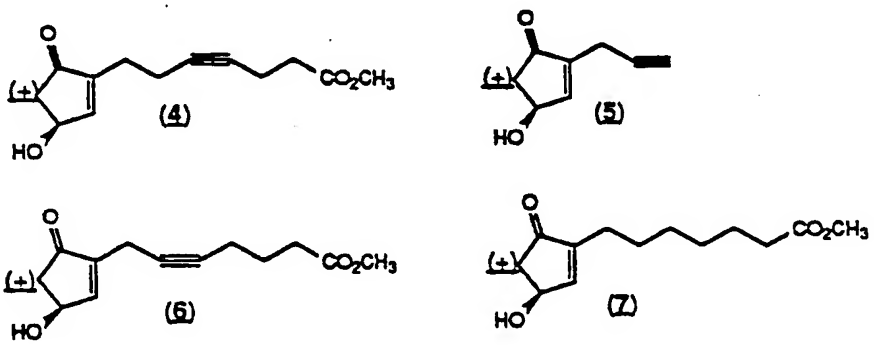
Two critical challenges were considered: a) enone (1S) which has the undesired (S)-configuration must be inverted with high stereospecificity to give the necessary (R)-enone (1R); b) over half of the product from the lipase reaction was 11-OAc-enone, (2R) which was predominantly (94%) the (R)-isomer. Methodology for enrichment of this material to usable optical purity (i.e. 98%) was desirable.

With respect to the first point, it was found that enone (1S) could be converted to (1R) via Mitsunobu chemistry.



In the present case, when (1S) of 99.9% (S) purity was submitted to Mitsunobu conditions (Bull. chem. Soc. Japan 44 3427, 1971) using formic acid as nucleophile and then immediate hydrolysis of the formate ester intermediate, a 91-94% chromatographed yield of inverted enone (1R) was obtained which was 99.3-99.6% (R) isomer. Therefore, only a maximum of 0.3 to 0.5% of racemization had occurred. This product was then converted to its triethyl silyl derivative, (3) in 94% yield after chromatography. Again, HPLC analysis on Chiracel OD column showed this material to be of identical optical purity to its precursor (99.3%R).

This enzymatic resolution method, coupled with the Mitsunobu alcohol inversion technology described here enalbes the preparation of either antipodes of the optically pure alcohol desired.



The following important features of the described process should be noted. No special apparatus or inert atmosphere are required for the lipase reactions since all reactions were carried out in organic solvents in the absence of water. A 0.1-0.2 kg scale kinetic resolution of racemic enone were easily performed in the laboratory. The four hydroxy enones shown above were also submitted to enzymatic resolution using PPL in vinyl acetate as described for compound (1). Greater than 92% ee (unoptimized) was achieved in all cases after 4 days reaction time. Chromatography is a necessary purification process for each hydroxy to acetate transformation since failure to remove acetate from the alcohol quantitatively will lead to effective racemization. All chemical and enzymatic reactions take place with a high degree of stereoselectivity and in high yield. Three batches of target Triethyl Silyl (3) were prepared: 40.25 g (99.3% R), 6.59 g (99.7% R) and 8.90 g (99.4% R).

It was found the all of the lipases were selective in acylating the R-isomer of the starting enone compound with (1). Amano-P lipase the most active catalyst. Using Amano-P as the enzyme source, relative rates of reaction were examined in five solvent systems using isopropenyl acetate as the acylating agent. Use of t-butyl methyl ether (TMBE) and aromatic solvents gave the highest rates. In addition to the lipase PPL, candida cylindracea (CC) lipase and a Pseudomonas Sp. (Amano-P) were studied both as their free powders and also immobilized on Amberlite XAD-8 resin, SIGMA Chem Co. In all cases, reaction at room temperature or 50 °C were extremely slow, usually <10% conversion after 5 days. However, with PPL immobilized on XAD-8 resin, a 25% conversion was achieved after 5 days at room temperature. Optimum conditions were established when excess vinyl acetate was employed in place of isopropenyl acetate and no solvent was used. Under these conditions reactions could be run at room temperature, were much faster and proceeded smoothly in 3-5 days. Moreover, the side products observed when isopropenyl acetate was employed as the acylating agent (due to interference by the methyl ester) were eliminated. The viability of the process was demonstrated on a 100 g scale.

A two-step process in which the acetate is removed by a purely chemical means and the recovered alcohol then resubmitted to the lipase acylation conditions was found to be most advantageous.

Referring to Scheme 2, when (2R) was treated with 2 equiv. of guanidine in CH_3OH, very rapid, clean conversion to the desired compound (1R) was observed in less than 5 minutes at 0 °C. In fact, when only

0.25 equiv. of guanidine were employed, the reaction profile and rate were identical to the stoichiometric case and compound (1R) (93% R) was recovered in 75-77% yield after chromatography. When this material was resubmitted to the action of PPL in vinyl acetate for 2 days, a 90% yield of compound (2R) was obtained with an enantiomeric excess of 99.6% (this represents a 98% conversion of available (R) alcohol (1R)). Deacylation via guanidine in methanol as described above provided the target (R)-enone (1R)). HPLC showed no racemization again during acetate removal. These results allow for complete conversion of both antipodes of (SC-37321) into chiral enone and all recovered non-enriched intermediates can be recycled to high optical purity (see Scheme 2).

Experimental Section

Column chromatography separations were performed by using Merck SiO_2 60 silica gel with ethyl acetate/hexane mixtures as eluants. TLC analyses were performed on Merck SiO_2 60 F254 precoated glass plates and were visualized by charring with phosphomolybdic acid in ethanol. Melting points (differential scanning calorimetry) were obtained on a Dupont 9900 Thermal Analyzer. NMR were recorded at room temperature in $CDCl_3$ using a General Electric QE-300 or Varian XL-400 spectrometer with TMS as internal standard. HPLC analyses were performed on Chiralcel OD, OA, or OC columns employing a chiral stationary phase (Daicel Chemical Industries) on a Waters Associates Model 590 solvent deliver system with Waters Intellingent Sample Processor (WISP). Optical rotations were measured with a Perkin-Elmer 241 polarimeter. IR spectra were recorded (as solutions in chloroform) on a Perkin-Elmer 681 spectrometer. CD spectra were recorded on a JASCO J-20 ORD/CD spectropolarimeter. UV spectra recorded (in CH_3OH) on a Beckman DU-7HS UV-Vis spectrophotometer.

Diethyl azodicarboxylate, triphenylphosphine, formic acid, guanidine carbonate, triethylsilyl chloride, sodium spheres were purchased from Aldrich and used without purification. Lipases: candida cylindracea (CC), porcine pancreatic lipase (PPL), pseudomonas species (PSp.) were purchased from Sigma Chemical Co. Amano P lipase was purchased from Amano Co. Isopropenyl acetate and vinyl acetate were purchased from Aldrich and fractionally distilled prior to use. All solvents were purchased from Burdich and Johnson and were reagent grade. CH_3OH was distilled from Mg; DMF was distilled at reduced pressure from magnesium sulfate, benzene and toluene were azeotropically distilled, chloroform was distilled from P_2O_5 and t-butyl methyl ether was distilled from benzophenone ketyl (all under inert atmosphere).

EXAMPLE 1

Preparation of Methyl 7-[3R-(acetyloxy)-5-oxo-1-cyclopenten-1-yl]-4Z-heptenoate (2R) and Methyl 7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate (1S) via enzymatic resolution

A mixture of 100.0 g of (0.42 mole) ±methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate (1), 100 g of porcine pancreatic lipase (14M units) and 2.5 L of distilled vinyl acetate were vigorously stirred at room temperature for 4 days. An additional 50-g portion of porcine pancreatic lipase was added and the mixture was stirred for one more day. The course of the reaction was monitored via HPLC on Chiralcel OD using 93:7 hexane:isopropanol as eluant until the enantiomeric excess of unreacted 3(S) alcohol was >99.8%. The crude mixture was then treated with 50 g of diatomaceous earth and filtered through a bed of diatomaceous earth. The filter cake was washed with 1.5 L of methylene chloride. The combined filtrates were concentrated under reduced pressure to give approximately 119 g of product mixture which contains predominantly 3(R)-acetate and 3(S) alcohol having R_f values of 0.25 and 0.49 respectively on TLC using 80% ethyl acetate/hexane. The product was chromatographed on silica gel using a solvent gradient of 50% to 100% ethyl acetate/hexane to give 50.5 g (43%) of (R) enriched methyl 7-[(3R-acetyloxy)-5-oxo-1-cyclopenten-1-yl]-4Z-heptenoate (2R) ^1H NMR ($CDCl_3$): δ 7.10 (m,1H, C_2H), 5.67 (m, 1H, C_3H), 5.30 (m, 2H, olefinic H), 3.68 (S, 3H, OCH_3), 2.86 (dd, 1H, $C_{4\beta}H$) J=6.5, 18.5 Hz, 2.36 (dd, 1H, $C_{4\alpha}H$) J=2.1, 18.5 Hz, 2.4-2.25 (m, 8H, CH_2); ^{13}C NMR ($CDCl_3$) δ 204.3, 173.1, 170.3, 151.8, 148.8, 129.4, 128.6, 71.3, 51.3, 41.3, 33.7, 24.7, 24.3, 22.6, 20.7 ppm; IR ($CHCl_3$) 3030, 3010, 1735, 1720, 1440, 1370, 1230 cm^{-1}; $[\alpha]_D^{20}$ +45.4° (-643.3° at 365 nM) (c 1.080 g/dL, $CHCl_3$); UV (CH_3OH) V_{max} = 220 nM; Anal. calc'd. for $C_{15}H_{20}O_5$ = C, 64.27; H, 7.19 Found: C, 64.24; H, 7.32 and 35.1 g (35%) of methyl 7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate (1R) ^1H NMR ($CDCl_3$) δ 7.10 (m, 1H, C_2H), 5.24 (m, 2H, olefinic), 4.93 (m, C_3H, 1H), 4.05 (b, 1H, OH), 3.68 (S, 3H, OCH_3), 2.80(dd, 1H, $C_{4\beta}H$) J = 6.0, 18.5 Hz, 2.4-2.2 (m, $C_{4\alpha}H$ + CH_2'S,9H); ^{13}C NMR δ 207.1, 174.1, 157.6, 146.9, 130.1, 128.8, 68.5, 51.9, 45.1, 34.2, 25.4, 24.6, 23.0 ppm; IR ($CHCl_3$) 3610, 3480 (broad), 3030, 3010, 1715 (shoulder at ~1730), 1440, 1230 cm^{-1}; $[\alpha]_D^{20}$ -13.3° (c 0.867 g/dL, CH_3Cl_3) (+1202° at 365 nM); UV (CH_3OH) λ_{max} = 221 nM; CD $[\vartheta]^{25}$ (nM) -11900 (320),

+64909 (224) (CH_3OH); Anal. calc'd. for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61; Found: C, 64.78; H, 7.74. HPLC (Chiralcel OD using 93:7 hexane in isopropanol as eluant) indicated the purified acetate (2R) was of 92% ee in R-isomer and that recovered alcohol (IS) was 99.4% ee in S-isomer.

EXAMPLE 2

Mitsunobu Inversion of Methyl 7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate (1S)

To a mixture of 7.14 g (30.0 mmol) of the title alcohol, 15.70 g (60.0 mmol) of triphenylphosphine in THF (100 mL) under argon was added formic acid via syringe. The solution was cooled to ~10°C in an ice bath. The reaction mixture was maintained at ≤15°C while 10.44 g (9.49 mL, 60.0 mmol) of diethyl azodicarboxylate was added dropwise via syringe. The pale yellow solution was warmed to room temperature and stirred at room temperature overnight. TLC (80% ethyl acetate/ hexane on silica gel) showed complete consumption of starting alcohol. The solvents were removed at reduced pressure to give a viscous oil. This was dissolved in 200 mL of t-butyl methyl ether (TBME) and to this was slowly added 400 mL of hexane and stirred at room temperature for 20 min. The mixture was filtered. The filter pad was washed with two 100-mL portions of 1:1 TBME:hexane. The combined filtrates were concentrated at reduced pressure to give 12.80 g of an amber oil which was dissolved in 300 mL of absolute methanol and stirred mechanically. To this was added gradually 200 g Woelm Super I (neutral) alumina. The mixture was stirred at room temperature for 5 hours to hydrolyze the formate ester intermediate. The mixture was filtered through a glass fritted funnel and the filter cake was washed with three 100-mL portions of CH_3OH. The combined filtrates were concentrated at reduced pressure to give ~12 g residue which was purified by flash chromatography on silica gel using gradient elution (30 to 75% ethyl acetate in hexane) to give 8.22 g of product which still contains 6-10% of 1,2-dicarbethoxyhydrazine (determined by ^1H NMR) which is removed in the subsequent step. An analytical sample was obtained by PTLC on 2000μ silica gel plates using two elutions of 65% ethyl acetate in hexane. The twice purified sample was identical to 3S-alcohol by normal phase HPLC, TLC, ^1H and ^{13}C NMR, UV and IR spectroscopy. $[\alpha]_D^{25}$ + 16.6° (c 1.024 g/dL, $CHCl_3$ (-1174° at 365 nM). CD $[\vartheta]^{25}$ (nM) -11900 (320) (negative maximum), +64909 (224) (positive maximum) (CH_3OH). HPLC on Chiralcel OD using 93/7 hexane/ isopropanol as eluant indicated that the ratio of 3R to 3S alcohols was 99.4/0.6.

EXAMPLE 3

Preparation of Methyl 7-(3R-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate (1R) from Methyl 7-[3R-(acetyloxy)-5-oxo-1-cyclopenten-1-yl]-4Z-heptenoate (2R) via deacylation

A stock solution of 0.5M guanidine in CH_3OH was prepared by adding 1.78 g (77.4 mmol) of 3X hexane washed sodium spheres to an ice-cooled CH_3OH (154 mL) under argon atmosphere. When an the sodium had reacted, 14.22 g (79.0 mmol) of guanidine carbonate was added. This was stirred at room temperature for 25 min and the mixture allowed to stand to settle out precipitated salts. In a separate flask was placed 12.8 g (45.6 mmol) of a ~93:7 mixture of R:S alcohols in 50 mL of absolute CH_3OH under argon. This was cooled to 0°C in an ice bath and to it was added via syringe 100 mL of 0.5M guanidine in CH_3OH prepared above, over ~5 min. This mixture was stirred at ~10°C for 5 min. TLC (80% ethyl acetate in hexane on silica gel) showed complete consumption of acetate. To the reaction mixture was then added 2.86 mL (3.0 g, 50.0 mmol) of glacial acetic acid to neutralize the guanidine. After stirring for 5 minutes, solvent was removed at reduced pressure to give a thick slurry. The residue was partitioned between 100 mL of water and 100 mL of 1:1 toluene: ethyl acetate. The aqueous layer was further extracted with two 50-mL portions of ethyl acetate. The combined organic layers were washed with two 50-mL portions of water, 50 mL of brine and dried over sodium sulfate. Removal of solvent at reduced pressure gave a deep amber oil which was purified by flash chromatography on silica gel with 50% ethyl acetate in hexane to give 8.06g of (1R) (77%) after exhaustive removal of solvent. ^1H and ^{13}C NMR were identical to previously isolated pure 3S-alcohol (1S). HPLC on Chiralcel OD using 93/7 hexane/isopropanol as eluant indicated a 93:7 R:S mixture of alcohols which showed that no racemization had taken place during deacylation.

EXAMPLE 4

Enzymatic Optical Enrichment of Methyl 7-(3R-hydroxy-5-oxo-cyclopenten-1-yl)-4Z-heptenoate (1R)

A mixture of 7.50 g (31.5 mmol) of 93:7 R:S alcohols, 7.50 g (99, 750 units) of porcine pancreatic lipase in 180 mL of distilled vinyl acetate was stirred vigorously at room temperature for 45 hours. HPLC of an aliquot on Chiralcel OD using 93:7 hexane:isopropanol showed excellent conversion of R alcohol (1R) to the corresponding acetate (2R). In fact, 98% of available R-alcohol had been consumed to give R-acetate with greater than 98.8% ee. The mixture was filtered through diatomaceous earth and the filter cake washed with two 100-L portions of methylene chloride. The combined filtrates were concentrated under reduced pressure to give 8.90 g of residue which was purified by chromatography on silica with 20% ethyl acetate in hexane as eluant. By this technique, 7.53 g (85%) of 98.8% ee R-acetate (2R) was obtained which was identical to previously isolated R-acetate by ^{1}H and ^{13}C NMR, HPLC and TLC.

EXAMPLE 5

Deacylation of Optically Enriched Methyl 7-(3R-acetyloxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate (2R)

To a room temperature solution of 7.47 g (26.6 mmol) of 98.8% ee 3R-acetate (2R) in 25 mL of absolute methanol under argon was added dropwise via syringe 5.2 mL (2.6 mmol) of stock 0.5M guanidine in methanol prepared above. The reaction was stirred at room temperature for 30 minutes. TLC on silica gel with 80% ethyl acetate in hexane showed complete conversion of acetate to free alcohol. The reaction was quenched by the addition of 314 μL (5.5 mmol) of glacial acetic acid. The solvent was removed at reduced pressure and the residue partitioned between 150 mL of 1:1 toluene/ethyl acetate and 50 mL of water. The aqueous layer was further extracted with 50 L of ethyl acetate. The combined organic layers were washed with two 25-mL portions of water, 25 mL of brine and dried over sodium sulfate to give 6.25 g of crude residue. This was purified by flash chromatography on silica gel with gradient elution of 50 to 75% ethyl acetate in hexane to give 4.89 g (77%) of R-alcohol (1R). HCLC on Chiralcel OD using 93:7 hexane:isopropanol as eluant indicated a 98.8% ee for the desired product. This product was identical to previously prepared 3R-alcohol by HPLC, ^{1}H and ^{13}C NMR and TLC.

EXAMPLE 6

Preparation of Methyl 7-[5-oxo-3R-[(triethylsilyl)oxy]-1 -cyclopenten-1-yl]-4Z-heptenoate (3)

To a 10°C solution of 34.60 g (0.136 mole) of 94% pure 3R-alcohol (1R), 34.3 g (0.34 mole) of triethylamine, 4.76 g (0.07 mole) of imidazole in 100 mL of DMF under nitrogen, was added dropwise via syringe 24.0 g (26.7 mL, 0.16 mole) of triethylsilylchloride. The mixture was warmed to room temperature for 4 hours. TLC (silica gel with 1:1 ethyl acetate:hexane as eluant) showed complete conversion of alcohol (R_f = .60). The mixture was poured into 300 mL of 1:1 toluene:hexane and this was washed with 300 mL of water followed by three 100-mL portions of water, then 50 mL of brine and dried over sodium sulfate. Removal of solvent at reduced pressure followed by in vacuo treatment at 2 x 10^{-2} torr at 50° for 2 hours gave 44.76 g crude product which was purified by chromatography on silica gel using a step gradient of 10 to 20% ethyl acetate in hexane. 40.25 g (84%) of purified TES-enone was obtained in this manner . HPLC on Chiralcel OD using 93:7 hexane:isopropanol indicated an enantiomer ratio (R/S) of 99.3:0.7. ^{1}H NMR (CDCl3): δ 7.04 (m, 1H, C_2H), 5.34 (m, 2H, cis olefin), 4.90 (m, 1H, C_3H), 3.68 (S, 3H, OCH_3), 2.75 (dd, 1H, $C_{4\beta}H$) J = 6.0, 18.0 Hz, 2.29 (dd, 1H, $C_{4\alpha}H$) obscured, 2.4-2.2 (m, 8H, CH_2), 1.0 (t, 9H, $3CH_3$) J = 8.0 Hz, 0.67 (q, 6H, $3CH_2$) J = 8Hz; ^{13}C NMR ($CDCl_3$): δ 206.3, 173.7, 157.3, 146.8, 130.3, 129.0, 69.1, 51.9, 45.9, 34.4, 25.4, 24.8, 23.2, 7.1, 5.1 ppm; IR ($CHCl_3$):3020, 3010, 1735, 1710, 1440, 1355, 1235, 1080 cm^{-1}; UV (CH_3OH) λ_{max} = 222 nM; $[\alpha]_D^{20}$ + 12.3° (c 0.814 g/dL, , $CHCl_3$) (-1018.4° at 365 nM); CD $[\vartheta]^{25}$ (nM) -12166 (315) (negative maximum); +66507 (224) (positive maximum) (CH_3OH); Anal. calc'd. for $C_{19}H_{32}O_4Si$: C, 64.75; H, 9.15; found: C, 64.67; H, 9.20.

EXAMPLE 7

Enzymatic Resolution of Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-heptanoate via PPL in Vinyl Acetate (7)

A mixture of 240 mg (1.0 mmol) of the title enone, 240 mg (3192 units) of porcine pancreatic lipase in 3 mL of distilled vinyl acetate was sealed and stirred at room temperature for a total of 9 days. Analysis on HPLC using Chiralcel OC at 50 °C using 90:10 hexane: isopropanol as eluant indicated that remaining alcohol was of >99.8% S-isomer. Resolution of the corresponding acetate was not possible under a variety of conditions. The reaction mixture was filtered through a bed of diatomaceous earth and the filter cake rinsed with methylene chloride. The combined filtrates were concentrated at reduced pressure to give 69 mg of crude residue which was purified by PTLC on silica gel (2000μ) using 65% ethyl acetate in hexane as eluant (R_f (ROH) = .30 and R_f (ROAc) = 0.61). In this manner was isolated 130 mg (46%) of methyl 7-(3R-acetyloxy-5-oxo-1-cyclopenten-1-yl)-heptanoate:^{1}H NMR ($CDCl_3$) δ 7.10 (m, C_2H, 1H), 5.66 (dm, C_3H, 1H), 3.68 (s, OCH_3, 3H), 2.87 (dd, $C_{4\beta}H$, 1H) J = 6, 19.0 Hz, 2.38 (dd, $C_{4\alpha}H$, 1H) J = 2.0, 19 Hz, 2.31 (t, CH_2,2H) J = 7.5 Hz, 2.21 (bt, 2H) J = 7.5 Hz, 2.10 (s, OAc, 3H), 1.62 (m, 2H), 1.35 (m, 4H); ^{13}C NMR ($CDCl_3$), δ 204.5, 173.8, 170.3, 151.4, 149.6, 70.2, 51.2, 41.3, 33.7, 28.7, 28.5, 26.9, 24.5, 24.3, 20.6 ppm; IR ($CHCl_3$) 3020, 3010, 1715 (shoulder at 1735), 1435,1370, 1240, 1025 cm^{-1}; UV (CH_3OH) λ_{max} = 221 nM; $[\alpha]_D^{20}$ +47.6° (c 0.871 g/dL, $CHCl_3$) (-649.3° at 365 nM); CD $[\vartheta]^{25}$ (nM) -7556 (315) (negative maximum), +49533 (224) (positive maximum); Anal. calc'd. for $C_{15}H_{22}O_5$: C, 63.80; H, 7.86; found: C, 63.32; H, 7.91 and then 99 mg (41%) of methyl 7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-heptanoate, mp = 60.1° (DSC), whose ^{1}H and ^{13}C NMR, IR, and UV spectra were identical to racemic alcohol. $[\alpha]_D^{20}$ -9.8° (c 1.072 g/dL, $CHCl_3$) (+1216.5° at 365 nM); CD $[\phi]^{25}$ (nM) -7556 (315) (negative maximum), +49533 (224) (positive maximum) (CH_3OH); anal. calc'd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39; found: C, 64.78; H, 8.52.

EXAMPLE 8

Enzymatic Resolution of Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-4-heptynoate via PPL in Vinyl Acetate (4)

A mixture of 116 mg (0.49 mmol) of title compound, 116 mo (1543 units) of porcine pancreatic lipase (PPL) in 3 mL of distilled vinyl acetate was sealed and stirred at room temperature for 7 days. Aliquots were removed every 24 hours for HPLC analysis on Chiralcel OC at 50 °C using 90/10 hexane/isopropanol as eluant. After 4 days, HPLC showed that remaining S-alcohol was of 96% ee in S-isomer. The product acetate could not be resolved under these conditions. The crude reaction mixture was filtered through diatomaceous earth and the filter pad was washed with methylene chloride. The combined filtrates were concentrated at reduced pressure to give 128 mg crude residue. Purification by PTLC on 2000μ silica plates (R_f (ROAc) = 0.55 and R_f (ROH) = 0.28) using 65% ethyl acetate/hexane as eluant gave 58 mg (43%) of methyl 7-(3R-acetyloxy-5-oxo-1-cyclopenten-1-yl)-4-heptynoate ^{1}H NMR ($CDCl_3$) δ 7.25 (m, C_2H, 1H), 5.80 (dm, C_3H, 1H), 3.70 (s, OCH_3, 3H), 2.88 (dd, $C_{4\beta}H$, 1H) J = 6.5, 19 Hz, 2.55-2.3 (m, $4CH_2$ + $C_{4\alpha}H$, 9H), 2.10 (S, OAc, 3H); ^{13}C NMR ($CDCl_3$) δ 204.7, 172.4, 170.5, 152.8, 147.8, 79.4, 79.4, 70.4, 41.7, 41.4, 33.7, 24.1, 20.9, 16.8, 14.6 ppm; IR ($CHCl_3$) 3020, 3010, 1735, 1717, 1437, 1370, 1240, 1027 cm^{-1} $[\alpha]_D^{20}$; + 41° (c 0.976 g/dL, $CHCl_3$) (-606.4° at 365 nM); CD $[\vartheta]^{25}$ (nM) -6022 (315) (negative maximum), +4668 (220 nM) (positive maximum) and 51 mg (45%) of methyl 7-(3S-hydroxy-5-oxo-1-cyclopentenyl)-4-heptynoate whose TLC, ^{1}H and ^{13}C NMR, IR were identical to racemic alcohol; $[\alpha]_D^{20}$ -16.7° (c 0.927 g/dL $CHCl_3$) (+984.4° at 365 nM); CD $[\vartheta]^{25}$ (nM) + 7690 (312), -55275 (225) (CH_3OH).

EXAMPLE 9

Enzymatic Resolution of 3-(3-hydroxy-5-oxo-1-cyclopenten-1-yl) propyne via PPL in Vinyl Acetate (5)

A mixture of 166 mg (1.22 mmol) of the title alcohol, 166 mg (2208 units) of porcine pancreatic lipase in 4 mL of distilled vinyl acetate was sealed and stirred at room temperature for a total of 7 days. Aliquots were removed periodically for assay on Chiralcel OA at 50°C using 96/4 hexane/isopropanol as eluant. After 7 days, HPLC indicated that remaining S-alcohol was of 98% ee and that the product acetate R/S isomers were again unresolved. The reaction mixture was filtered through diatomaceous earth and the filter cake washed with methylene chloride. The combined filtrates were concentrated at reduced pressure to give 205 mg of crude residue which was purified by PTLC on 2000μ silica gel plates using 65% ethyl acetate in hexane as eluant (R_f (ROAc) = 0.60 and R_f (ROH) = 0.37). In this manner was isolated 76 mg (35%) of 3-(3R-acetyloxy-5-oxo-1-cyclopenten-1-yl)propyne: ^{1}H NMR ($CDCl_3$) δ 7.44 (q, C_2H, 1H) J = 2.1 Hz, 5.75 (m, C_3H, 1H), 3.13 (q, CH_2, 2H) J = 2.1 Hz 2.93 (dd, $C_{4\beta}$H, 1H) J = 2.2, 19.0 Hz, 2.21 (t, C≡C-H, 1H) J = 5.3 Hz, 2.11 (s, OAc, 3H); ^{13}C NMR ($CDCl_3$) δ 202.6, 170.2, 153.5, 144.7, 78.8, 71.2, 69.8, 41.6, 20.7, 15.2 ppm; IR ($CHCl_3$): 3300, 3020, 3010, 1740, 1720, 1640, 1410, 1370, 1240, 1025 cm^{-1}; UV (CH_3OH) λ_{max} = 219 nM; $[\alpha]_D^{20}$ 52.2° (c 0.928 g/dL $CHCl_3$) (-713° at 365 nM); CD $[\vartheta]^{25}$ (nM) -3968 (319), +27494 (216) (CH_3OH), no elemental analysis, and 65 mg (48%) of 3-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)propyne whose ^{1}H NMR, IR, and UV were identical to racemic alcohol; $[\alpha]_D^{20}$ -8.7° (c 0.863 g/dL, $CHCl_3$) (+1693° at 365 nM; CD $[\vartheta]^{25}$ (nM) + 9923 (318 nM), -50781 (224) (CH_3OH).

EXAMPLE 10

Enzymatic Resolution of Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-5Z-heptenoate via PPL in Vinyl Acetate (6)

A mixture of 83 mg (0.35 mmol) of the title alcohol, 83 mg (1104 units) of porcine pancreatic lipase in 3.0 mL of distilled vinyl acetate was sealed and stirred at room temperature for a total of 7 days. Aliquots were removed every 24 hours for HPLC analysis on Chiralcel OD using 97/3 hexane/isopropanol as eluant. After 7 days, HPLC indicated that remaining alcohol had a 96/4 S/R in isomer ratio and that this ratio was still improving. Nevertheless, the mixture was filtered through bed of diatomaceous earth and the filter pad was rinsed with methylene chloride. The combined filtrates were concentrated at reduced pressure to give 86 mg crude residue. PTLC on 2000μ silica gel plates using 65% ethyl acetate in hexane as eluant gave 45 mg (R_f = 0.61, 46%) of methyl 7- (3R-acetyloxy-5-oxo-1-cyclopentene-1-yl)-5Z-heptenoate: ^{1}H NMR ($CDCl_3$) δ 7.12 (m, C_2H, 1H), 5.72 (dm, C_3H, 1H), 5.47 (m, olefinic H, 2H), 3.68 (s, OCH_3, 3H), 2.96 (m, bis allylic CH_2), 2.89 (dd, $C_{4\beta}$H, 1H) J = 6.5, 19.0 Hz, 2.48 (dd, $C_{4\alpha}$H, 1H) J = 6.5, 19.0 Hz, 2.48 (dd, C_{4a}H, 1H) J = 2.1, 19.0 Hz, 2.31 (t, CH_2CO_2, 2H) J = 10.1 Hz, 2.10 (m, 2H), 2.10 (s, OAc, 3H), 1.70 (quint, isolated CH_2, 2H) J = 7.5 Hz; IR ($CHCl_3$) 3020, 3010, 1715 (shoulder at ~1735), 1435, 1370, 1240, 1025 cm^{-1}; $[\alpha]_D^{20}$ +47.1° (c 0.935 g/dL, $CHCl_3$) (-649.2° at 365 nM); UV (CH_3OH) λ_{max} = 218 nM; CD $[\vartheta]^{25}$ (nM) -7556 (315), +49533 (224) (CH_3OH); anal. calc'd. for $C_{15}H_{20}O_5$: C, 63.81; H, 7.14; found: C, 63.65; H, 7.04 and then 33 mg (R_f = 0.34, 40%) of methyl 7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-5Z-heptenoate whose ^{1}H NMR, IR, TLC were identical to racemic alcohol; $[\alpha]_D^{20}$ -19.9° (c 0.627 g/dL, $CHCl_3$) (+1031° at 365 nM); CD $[\vartheta]^{25}$ (nM) + 24731 (314), -175176 (225) (CH_3OH), no elemental analysis.

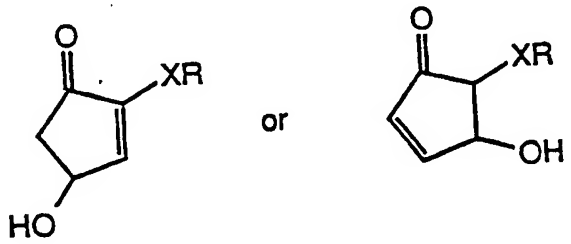
EXAMPLE 11

Immobilization of PSL Using XAD-8 Resin

A solution of PSL (100 mg) in 10 ml of 0.05 M phosphate buffer solution (pH = 7.0) was mixed with 10 g of polystyrene beads (XAD-8 from Sigma). The suspension was stirred overnight at 8°°C. Most of the water was removed by pipet, the residue was dried over a cacuum pump (rt, 24 hours) to give the immobilized enzyme which was directly used for transesterification.

Claims

1. A method for resolution of a compound of the formula:



wherein X represents alkyl, alkenyl or alkynyl of from 2 to 10 carbon atoms, optionally including a S or O atom at the 2, 3, 4, 5, 6, 7, 8 or 9 postion, and R is $-CH_2OR_1$ wherein R_1 is hydrogen, alkyl of 1 to 6 carbon atoms, tetrahydropyranyl, ethoxyethyl, acyl, or $-CO_2R_2$, or $(R_2)_3Si$ wherein R_3 is independently alkyl of 1-10 carbon atoms or aryl, wherein R_2 is alkyl of 1 to 6 carbon atoms, said method comprising:

mixing said compound with a lipase in the presence of an acylating reagent to thereby obtain the corresponding S alcohol and R acetat; and

treating said S alcohol with diethylazocarboxylate, triphenyl phosphine and formic acid followed by hydrolysis of the intermediate formate ester with neutral alumina and methanol to obtain the corresponding R alcohol with essentially complete inversion.

2. The method of Claim 1 wherein the acylating reagent is selected from the group consisting of isopropenyl acetate, isopropenyl valerate, vinyl acetate, vinyl propionate and vinyl valerate.

3. The method of Claim 2 wherein the lipase is selected from the group consisting of Pseudomonas species (PSL, Type XIII), porcine pancrease (PPL, Type II), candida cylindracea (CCL, Type VII), amano P, ANL, aspergillus niger, or ChE cholesterol esterase.

4. The method of Claim 1 wherein the lipase is porcine pancreas (PPL, Type II) or amano P.

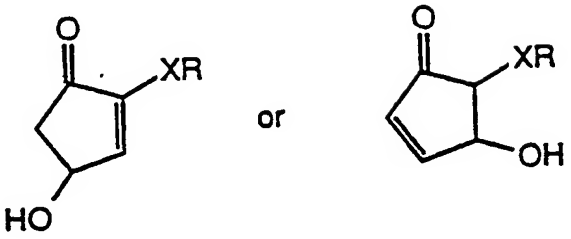
5. The method of Claim 4 wherein the acylating reagent is isopropenyl acetate or vinyl acetate.

6. The method of Claim 1 wherein the lipase is porcine pancreas (PPL), the acylating reagent is vinyl acetate and said compound is:
Methyl 7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate (1S)
Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-4-heptenoate (4)
3-(3-hydroxy-5-oxo-1-cyclopenten-1-yl) propyne (5)
Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-5Z-heptenoate (6) or
Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-heptenoate (7).

7. The method of Claim 6 wherein said compound is methyl-7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate.

8. The method of Claim 6 wherein the lipase is immobilized on a support.

9. A method for resolution of a compound of the formula:



wherein X represents alkyl, alkenyl or alkynyl of from 2 to 10 carbon atoms, optionally including a S or O atom at the 2, 3, 4, 5, 6, 7, 8 or 9 position and R is $-CH_2OR_1$ wherein R_1 is hydrogen, alkyl of 1 to 6 carbon atoms, tetrahydropyranyl, ethoxyethyl, acyl or $-CO_2R_2$ wherein R_2 is alkyl of 1 to 6 carbon atoms, said method comprising:

mixing said compound with a lipase in the presence of an acylating reagent to thereby obtain the corresponding S alcohol and R acetate:

treating said R acetate compound with guanidine and an alcohol to obtain the corresponding R alcohol;

mixing said R alcohol with a lipase in the presence of an acylating reagent to thereby obtain the corresponding R acetate; and

treating said R acetate with guanidine and an alcohol to thereby obtain the optically pure R alcohol compound.

10. The method of Claim 9 wherein the acylating reagent is selected from the group consisting of isopropenyl acetate, isopropenyl valerate, vinyl acetate, vinyl propionate and vinyl valerate.

11. The method of Claim 10 wherein the lipase is selected from the group consisting of Pseudomonias species (PSL, Type XIII), porcine pancreas (PPL, Type II), candida cylindracea (CCL, Type VII) and amano P.

12. The method of Claim 9 wherein the lipase is porcine pancreas (PPL, Type II) or amano P.

13. The method of Claim 12 wherein the acylating reagent is isopropenyl acetate or vinyl acetate.

14. The method of Claim 9 wherein the lipase is porcine pancreas (PPL), the acylating reagent is vinyl acetate and said compound is:
Methyl 7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate (1S)
Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-4-heptenoate (4)
3-(3-hydroxy-5-oxo-1-cyclopenten-1-yl) propyne (5)
Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-5Z-heptenoate (6) or
Methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-heptenoate (7).

15. The method of Claim 14 wherein said compound is methyl-7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoate.

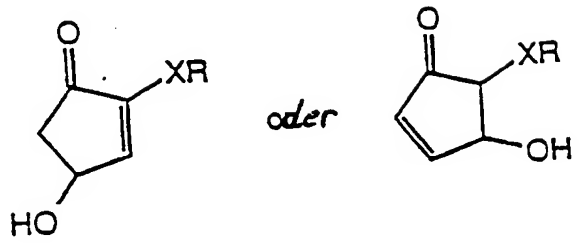
16. The method of Claim 6 wherein the lipase is immobilized on a support.

17. The method of Claim 1 wherein the lipase is mixed with the acylating reagent in the presence of a solvent selected from the group consisting of $CHCl_3$, benzene, toluene, t-butylmethyl ether, tetrahydrofuran, diethyl ether or hexane.

18. The method of Claim 9 wherein the lipase is mixed with the acylating reagent in the presence of a solvent selected from the group consisting of $CHCl_3$, benzene, toluene, t-butylmethyl ether, tetrahydrofuran, diethyl ether or hexane.

Patentansprüche

1. Ein Verfahren zur Aufspaltung einer Verbindung der Formel:



worin X Alkyl, Alkenyl oder Alkinyl mit 2 bis 10 Kohlenstoffatomen darstellt, das gegebenenfalls in der 2, 3, 4, 5, 6, 7, 8 oder 9-Position ein S- oder O-Atom enthält, und R $-CH_2OR_1$ bedeutet, worin R_1 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Tetrahydropyranyl, Ethoxyethyl, Acyl oder $-CO_2R_2$ oder $(R_2)_3Si$ bedeutet, worin R_3 unabhängig voneinander Alkyl mit 1 bis 10 Kohlenstoffatomen oder Aryl bedeutet, worin R_2 Alkyl mit 1 bis 6 Kohlenstoffatomen ist, wobei dieses Verfahren folgende Stufen umfaßt:
Vermischen dieser Verbindung mit einer Lipase in Gegenwart eines Acylierungsmittels, wobei man den entsprechenden S-Alkohol und das R-Acetat erhält, und
Behandlung dieses S-Alkohols mit Diethylazocarboxylat, Triphenylphosphin und Ameisensäure mit anschließender Hydrolyse des Zwischenprodukt-Ameisensäureesters mit neutraler Tonerde und Methanol unter Erzielung des entsprechenden R-Alkohols mit im wesentlichen vollständiger Inversion.

2. Das Verfahren nach Anspruch 1, worin das Acylierungsmittel ausgewählt ist aus der Gruppe bestehend aus Isopropenylacetat, Isopropenylvalerat, Vinylacetat, Vinylpropionat und Vinylvalerat.

3. Das Verfahren nach Anspruch 2, worin die Lipase ausgewählt ist aus der Gruppe bestehend aus Pseudomonas-Spezies (PSL, Typ XIII), Porcin-Pancreas (PPL, Typ II), Candida cylindracea (CCL, Typ VII), Amano P, ANL, Aspergillus niger oder ChE-Cholesterinesterase.

4. Das Verfahren nach Anspruch 1, worin die Lipase Porcin-Pancreas (PPL, Typ II) oder Amano P ist.

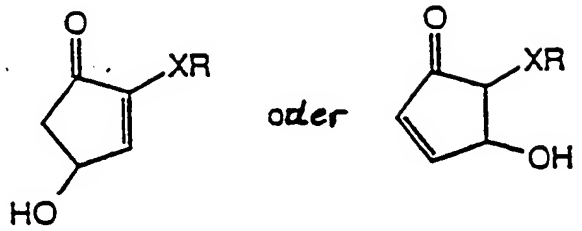
5. Das Verfahren nach Anspruch 4, worin das Acylierungsmittel Isopropenylacetat oder Vinylacetat ist.

6. Das Verfahren nach Anspruch 1, worin die Lipase Porcin-Pancreas (PPL), das Acylierungsmittel Vinylacetat und die Verbindung
Methyl-7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoat (1S),
Methyl-7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-4-heptenoat (4),
3-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl-propyn (5),
Methyl-7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-5Z-heptenoat (6) oder
Methyl-7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-heptenoat (7)
ist.

7. Das Verfahren nach Anspruch 6, worin diese Verbindung Methyl-7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoat ist.

8. Das Verfahren nach Anspruch 6, worin die Lipase auf einem Träger immobilisiert ist.

9. Ein Verfahren zur Aufspaltung einer Verbindung der Formel:



worin X Alkyl, Alkenyl oder Alkinyl mit 2 bis 10 Kohlenstoffatomen darstellt, das gegebenenfalls in der 2, 3, 4, 5, 6, 7, 8 oder 9-Position ein S- oder O-Atom enthält und R $-CH_2OR_1$ bedeutet, worin R_1 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Tetrahydropyranyl, Ethoxyethyl, Acyl oder $-CO_2R_2$ bedeutet, worin R_2 Alkyl mit 1 bis 6 Kohlenstoffatomen ist, wobei dieses Verfahren folgende Stufen umfaßt:
Mischen dieser Verbindung mit einer Lipase in Gegenwart eines Acylierungsmittels, wobei man den entsprechenden S-Alkohol oder das R-Acetat erhält;
Behandlung dieser R-Acetatverbindung mit Guanidin und einem Alkohol unter Erzielung des entsprechenden R-Alkohols;
Mischen dieses R-Alkohols mit einer Lipase in Gegenwart eines Acylierungsmittels unter Erzielung des entsprechenden R-Acetats und
Behandeln dieses R-Acetats mit Guanidin und einem Alkohol unter Erzielung der optisch reinen R-Alkoholverbindung.

10. Das Verfahren nach Anspruch 9, worin das Acylierungsmittel ausgewählt ist aus der Gruppe bestehend aus Isopropenylacetat, Isopropenylvalerat, Vinylacetat, Vinylpropionat und Vinylvalerat.

11. Das Verfahren nach Anspruch 10, worin die Lipase ausgewählt ist aus der Gruppe bestehend aus Pseudomonas-Spezies (PSL, Typ XIII), Porcin-Pancreas (PPL, Typ II), Candida cylindracea (CCL, Typ VII) und Amano P.

12. Das Verfahren nach Anspruch 9, worin die Lipase Porcin-Panreas (PPL, Typ II) oder Amano P. ist.

13. Das Verfahren nach Anspruch 12, worin das Acylierungsmittel Isopropenylacetat oder Vinylacetat ist.

14. Das Verfahren nach Anspruch 9, worin die Lipase Porcin-Pancreas (PPL), das Acylierungsmittel Vinylacetat und die Verbindung
Methyl-7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoat (1S),
Methyl-7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-4-heptenoat (4),
3-(3-Hydroxy-5-oxo-1-cyclopenten-1-yl)-propyn (5),
Methyl-7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-5Z-heptenoat (6) oder
Methyl-7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-heptenoat (7)
ist.

15. Das Verfahren nach Anspruch 14, worin diese Verbindung Methyl-7-(3S-hydroxy-5-oxo-1-cyclopenten-1-yl)-4Z-heptenoat ist.

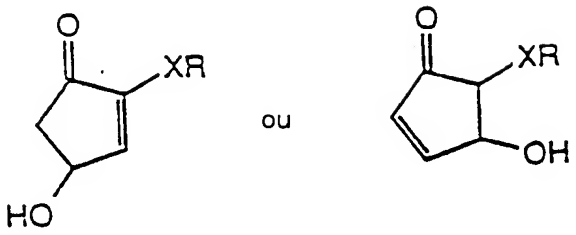
16. Das Verfahren nach Anspruch 6, worin die Lipase auf einem Träger immobilisiert ist.

17. Das Verfahren nach Anspruch 1, worin die Lipase mit dem Acylierungsmittel in Gegenwart eines Lösungsmittels vermischt wird, ausgewählt aus der Gruppe bestehend aus $CHCl_3$, Benzol, Toluol, t-Butylmethylether, Tetrahydrofuran, Diethylether oder Hexan.

18. Das Verfahren nach Anspruch 9, worin die Lipase mit dem Acylierungsmittel in Gegenwart eines Lösungsmittels vermischt wird, ausgewählt aus der Gruppe bestehend aus $CHCl_3$, Benzol, Toluol, t-Butylmethylether, Tetrahydrofuran, Diethylether oder Hexan.

Revendications

1. Procédé de résolution d'un composé de formule :



formules dans lesquelles X représente un groupe alkyle, alcényle ou alcynyle ayant 2 à 10 atomes de carbone, et comprenant éventuellement un atome de S ou de O en position 2, 3, 4, 5, 6, 7, 8 ou 9, et R représente un groupe $-CH_2OR_1$, dans lequel R_1 représente un atome d'hydrogène, un groupe alkyle ayant 1 à 6 atomes de carbone, tétrahydropyrannyle, éthoxyéthyle, acyle, ou $-CO_2R_2$ ou $(R_3)_3Si$, formules dans lesquelles chaque R_3 représente, indépendamment, un groupe alkyle ayant 1 à 10 atomes de carbone ou un groupe aryle et R_2 représente un groupe alkyle ayant 1 à 6 atomes de carbone, ledit procédé comprenant :

le mélangeage dudit composé avec une lipase en présence d'un réactif à rôle d'acylation afin d'obtenir ainsi l'alcool S et l'acétate R correspondants ; et

le traitement dudit alcool S par de l'azocarboxylate de diéthyle, de la triphénylphosphine et de l'acide formique, opération suivie de l'hydrolyse du formiate intermédiaire à l'aide d'alumine neutre et de méthanol, pour obtenir avec une inversion essentiellement complète l'alcool R correspondant.

2. Procédé selon la revendication 1, dans lequel le réactif à rôle d'acylation est choisi dans l'ensemble consistant en l'acétate d'isopropényle, le valérate d'isopropényle, l'acétate de vinyle, le propionate de vinyle et le valérate de vinyle.

3. Procédé selon la revendication 2, dans lequel la lipase est choisie dans l'ensemble consistant en l'espèce Pseudomonas (PSL, type XIII), un pancréas de porc (PPL, type II), candida cylindracea (CCL, type VII), amano P, ANL, aspergillus niger ou une estérase de cholestérol ChE.

4. Procédé selon la revendication 1, dans lequel la lipase est ou provient d'un pancréas de porc (PPL, type II) ou est amano P.

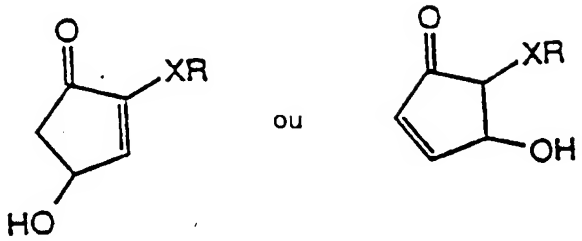
5. Procédé selon la revendication 4, dans lequel le réactif à rôle d'acylation (ou agent d'acylation) est l'acétate d'isopropényle ou l'acétate de vinyle.

6. Procédé selon la revendication 1, dans lequel la lipase provient de pancréas de porc (PPL), le réactif à rôle d'acylation est l'acétate de vinyle et ledit composé est :
le 7-(3S-hydroxy-5-oxo-1-cyclopentène-1-yl)-4Z-hepténoate de méthyle (1S),
le 7-(3-hydroxy-5-oxo-1-cyclopentène-1-yl)-4-hepténoate de méthyle (4),
le 3-(3-hydroxy-5-oxo-1-cyclopentène-1-yl)propyne (5),
le 7-(3-hydroxy-5-oxo-1-cyclopentène-1-yl)-5Z-hepténoate de méthyle (6) ou
le 7-(3-hydroxy-5-oxo-1-cyclopentène-1-yl)-hepténoate de méthyle (7).

7. Procédé selon la revendication 6, dans lequel ledit composé est le 7-(3S-hydroxy-5-oxo-1-cyclopentène-1-yl)-4Z-hepténoate de méthyle.

8. Procédé selon la revendication 6, dans lequel la lipase est immobilisée sur un support.

9. Procédé de résolution d'un composé de formule :



formules dans lesquelles X représente un groupe alkyle, alcényle ou alcynyle ayant 2 à 10 atomes de carbone comprenant éventuellement un atome de O ou de S en position 2, 3, 4, 5, 6, 7, 8 ou 9 et R représente $-CH_2OR_1$, formule dans laquelle R_1 représente un atome d'hydrogène, un groupe alkyle ayant 1 à 6 atomes de carbone, un groupe tétrahydropyrannyle, éthoxyéthyle, acyle ou $-CO_2R_2$, formule dans laquelle R_2 représente un groupe alkyle ayant 1 à 6 atomes de carbone, ledit procédé comprenant :

le mélangeage de ce composé avec une lipase en présence d'un réactif à rôle d'acylation afin d'obtenir ainsi l'alcool S et l'acétate R correspondants ;

le traitement de l'acétate R avec de la guanidine et un alcool pour obtenir l'alcool R correspondant ;

le mélangeage de cet alcool R avec une lipase en présence d'un réactif à rôle d'acylation pour obtenir ainsi l'acétate R correspondant ; et

le traitement de cet acétate R avec de la guanidine et un alcool pour obtenir ainsi l'alcool R optiquement pur.

10. Procédé selon la revendication 9, dans lequel le réactif à rôle d'acylation est choisi dans l'ensemble consistant en l'acétate d'isopropényle, le valérate d'isopropényle, l'acétate de vinyle, le propionate de vinyle et le valérate de vinyle.

11. Procédé selon la revendication 10, dans lequel la lipase est choisie dans l'ensemble consistant en de la lipase de Pseudomonas species (PSL, type XIII), du pancréas de porc (PPL, type II), candida cylindracea (CCL, type VII) et amano P.

12. Procédé selon la revendication 9, dans lequel la lipase est de la lipase de pancréas de porc (PPL, type II) ou amano P.

13. Procédé selon la revendication 12, dans lequel le réactif à rôle d'acylation est l'acétate d'isopropényle ou l'acétate de vinyle.

14. Procédé selon la revendication 9, dans lequel la lipase est la lipase provenant de pancréas de porc (PPL), le réactif à rôle d'acylation est l'acétate de vinyle, et ledit composé est :
le 7-(3S-hydroxy-5-oxo-1-cyclopentène-1-yl)-4Z-hepténoate de méthyle (1S),
le 7-(3-hydroxy-5-oxo-1-cyclopentène-1-yl)-4-hepténoate de méthyle (4),
le 3-(3-hydroxy-5-oxo-1-cyclopentène-1-yl)propyne (5),
le 7-(3-hydroxy-5-oxo-1-cyclopentène-1-yl)-5Z-hepténoate de méthyle (6) ou
le 7-(3-hydroxy-5-oxo-1-cyclopentène-1-yl)-hepténoate de méthyle (7).

15. Procédé selon la revendication 14, dans lequel ledit composé est le 7-(3S-hydroxy-5-oxo-1-cyclopentène-1-yl)-4Z-hepténoate de méthyle.

16. Procédé selon la revendication 6, dans lequel la lipase est immobilisée sur un support.

17. Procédé selon la revendication 1, dans lequel la lipase est mélangée avec le réactif à rôle d'acylation en présence d'un solvant choisi dans l'ensemble consistant en $CHCl_3$, le benzène, le toluène, l'éther de t-butyle et de méthyle, le tétrahydrofuranne, l'éther diéthylique ou l'hexane.

18. Procédé selon la revendication 9, dans lequel la lipase est mélangée avec le réactif à rôle d'acylation, en présence d'un solvant choisi dans l'ensemble consistant en $CHCl_3$, le benzène, le toluène, l'éther de t-butyle et de méthyle, le tétrahydrofuranne, l'éther diéthylique ou l'hexane.